Reactions of Isatoic Anhydride as a Masked Isocyanate with Oxygen and Nitrogen Nucleophiles—Kinetics and Mechanism

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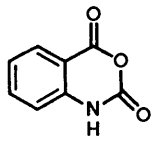
The hydrolysis of isatoic anhydride **1**, its 5-nitro **7**; (X = NO_2, R = H) and *N*-methyl derivatives in water at 25 °C occurs mainly *via* direct HO^- attack on the neutral substrate. At high pH where **1** and **7** (X = NO_2, R = H) are ionized, the *o*-carboxyphenyl isocyanate **8b** is formed in equilibrium with the anion **8a**, and this undergoes a competing reaction with HO^- (but at a slower rate). Reaction with amines at the anhydride carbonyl (C-4) which occurs at pH < 10 is characterized by a β_{nuc} value of +1.0 but is highly sensitive to the steric bulk of the attacking amine. In consequence reaction at the isocyanate in the anion **8** (X = H) is only important with bulky amines. With the 5-nitro derivative (pK_a 6.7), reaction with the conjugate base can be measured even with non-hindered bases; these yield a β_{nuc} value of 0.31, providing strong evidence that reaction occurs *via* the isocyanate **8b** (X = NO_2). The implications for heterocyclic synthesis starting from isatoic anhydride are considered.

Isatoic anhydride **1** {benz[*d*][1,3]oxazine-2(1*H*),4-dione} can be regarded as a cyclic anhydride of a carbamic and a carboxylic acid. The acyclic analogues **2** are not well characterized although proposed as intermediates in the reaction of isocyanates with carboxylic acids (leading ultimately on decarboxylation to amides).[1] The anhydrides **2** are expected to undergo rapid E1cB-type elimination to give isocyanate intermediates in aqueous solution as judged from related aryloxy carbamates with good leaving groups.[2,3] With isatoic anhydride **1** direct nucleophilic attack can occur at C-2 or C-4 in addition to ring opening to give an isocyanate. Indeed, extensive product studies[4] and a limited kinetic analysis[5] (neither of which involved pH control) confirm that both products **3** (by attack at C-4 followed by decarboxylation) and **4** (attack at C-2) are formed, in ratios which are highly dependent on the nucleophile and the reaction conditions.



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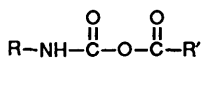

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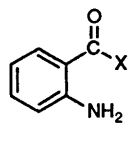

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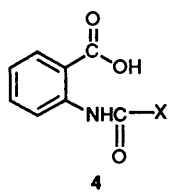

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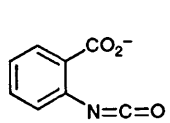
As such **1**, therefore, may have potential as a 'blocked isocyanate' in which the activity of this functional group is moderated by internal trapping by the *ortho*-CO_2^- group in **5**. The reversible addition of imidazole and other nitrogen heterocycles to isocyanates provides an intermolecular analogue.[6] However, the elimination–addition pathway need not be dominant as demonstrated[7] in the reactions of 5-nitrocoumaran-2-one **6** with nucleophiles; although **6** shows enhanced reactivity (relative to acyclic analogues) and the E1cB mechanism *via* a ketene intermediate is an 'allowed' process, direct nucleophilic attack at the carbonyl group is observed rather than the elimination–addition pathway.



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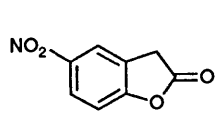

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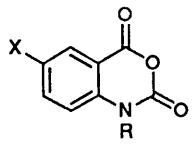

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We now report on the competing reactions of **1** [and its *N*-methyl (**7**; R = Me, X = H) and 5-nitro (**7**; R = H, X = NO_2) derivatives] with hydroxide ion and amines and on the existence of a reaction pathway *via* **5**.

Results and Discussion

Hydrolysis of Isatoic Anhydride and N-*Methylisatoic Anhydride.*—In order to establish the background reactivity of **1** and **7** (R = Me, X = H) with water and hydroxide ion, their reactivities were examined in aqueous solution at 25 °C (μ = 1.0, KCl). The rate constants obtained are plotted as a function of pH in Fig. 1.

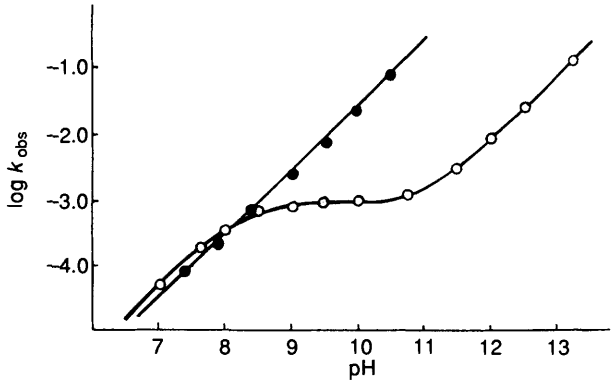


Fig. 1. The pH–log rate profile for the hydrolysis of isatoic anhydride (○) and *N*-methylisatoic anhydride (●) at 25 °C (μ = 1.0, KCl).

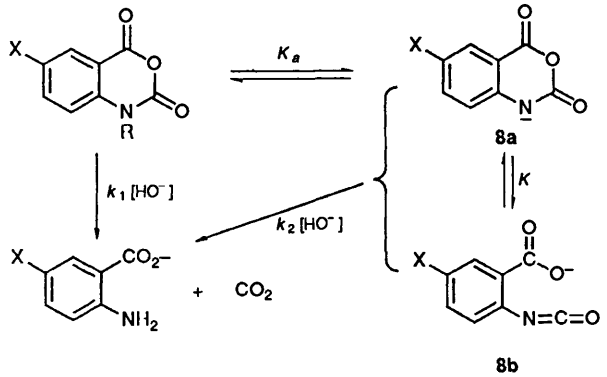
Both substrates show clearly different behaviour. The reactivity of the *N*-methyl substrate is proportional to [HO^-] and the plot in Fig. 1 follows eqn. (1), with $k_{HO^-} = 3.6 \times 10^2$

$$k_{obs} = k_{HO^-}[HO^-] \quad (1)$$

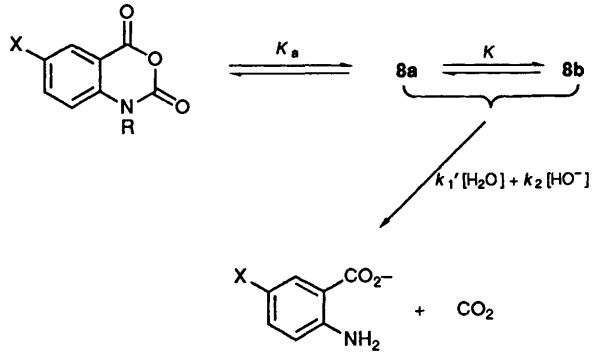
$dm^3\ mol^{-1}\ s^{-1}$. Isatoic anhydride itself shows a more complex pH–rate profile with two regions where k_{obs} is proportional to [HO^-], separated by a region (pH *ca.* 9–10.5) where k_{obs} is independent of pH. The observed behaviour is fitted by eqn. (2); the theoretical curve drawn in Fig. 1 assumes the

$$k_{obs} = \frac{k_1 K_w}{a_H + K_a} + k_2 K[HO^-] \quad (2)$$

following values for the constants: $k_1 = 5.6 \times 10^2$ $dm^3\ mol^{-1}\ s^{-1}$, $K_a = 5.62 \times 10^{-9}$ and $k_2K = 6.1 \times 10^{-1}$ $dm^{-3}\ mol^{-1}\ s^{-1}$. Two kinetically equivalent mechanisms to account for this behaviour are presented (Schemes 1 and 2). Both imply the



Scheme 1.



Scheme 2.

formation of the conjugate base **8a** which can undergo ring-opening to give the *o*-carboxy isocyanate **8b**. In Scheme 1 the neutral isatoic anhydride is the reactive species at lower pH, while the anion **8** is relatively unreactive; only at high pH is reaction of the anion **8a** (or more likely the isocyanate **8b** with HO^- apparent. In Scheme 2 the neutral material is unreactive while the conjugate base **8** undergoes both spontaneous (or water-catalysed) reaction and reaction with HO^-.

These mechanisms can clearly be distinguished by taking into account the results for the *N*-methyl derivative **7** (R = Me, X = H), which cannot ionize. The reactivity of **7** (R = Me, X = H) with HO^- ($k_{HO^-} = 3.6 \times 10^2$ $dm^3\ mol^{-1}\ s^{-1}$) is almost the same (5.6×10^2 $dm^3\ mol^{-1}\ s^{-1}$) as that calculated for k_1 (Scheme 1), indicating that the derived value is not unreasonable when direct attack on the neutral substrate (Scheme 1) is assumed.

Scheme 1 also implies that isatoic anhydride is ionized at pH > 8. This was apparent spectrophotometrically and measuring the change in absorbance (*A*) at 320 nm as a function of pH gave a pK_a of 8.25 (see Fig. 2). Since isatoic anhydride is reactive in water in this pH region the absorbance at 0% reacted was obtained by extrapolation in each case. The acidity constant (K_a, Scheme 1) required to fit the kinetic scheme and that determined spectrophotometrically are thus identical.

The reaction of hydroxide ion noted at high pH could be with the anion of the heterocycle itself **8a** or with the open-chain tautomer **8b**. If the latter is correct (see also below) then the equilibrium between the cyclic material **8a** and the isocyanate **8b** must lie very much to the side of the former (*i.e.* $K \ll 1$) since phenyl isocyanate reacts rapidly with HO^- (the rate of reaction of phenyl isocyanate with water is 3.39×10^{-2} s^{-1} and with HO^- is 1.17×10^3 $dm^3\ mol^{-1}\ s^{-1}$ at 25 °C).[6,7] Assuming a ρ value of 2.6 for the HO^- reaction with aryl isocyanates,[8] a second-order rate constant can be estimated for the reaction of the *o*-carboxy carbonate **8b** (X = H) with HO^-. On this basis *K* is estimated to be *ca.* 1/2000.

Table 1. Observed second-order rate constants for the reaction of *N*-methylisatoic anhydride (**7**; R = Me, X = H) with amines.[a]

Amine	pK_a	$k_{amine}/dm^3\ mol^{-1}\ s^{-1}$
GlyOEt	7.90	0.40
$MeNH_2$	10.62	145
$EtNH_2$	10.65	20.4
Pr^iNH_2	10.63	9.02
Me_2NH	10.64	8.34
Et_2NH	10.98	15.4
NH_3	9.33	12.6
Piperidine	11.42	33.6

[a] Data obtained at pH 8.0 (where the hydrolysis rate is 2.95×10^{-4} s^{-1}) at 25 °C (μ = 1.0, KCl).

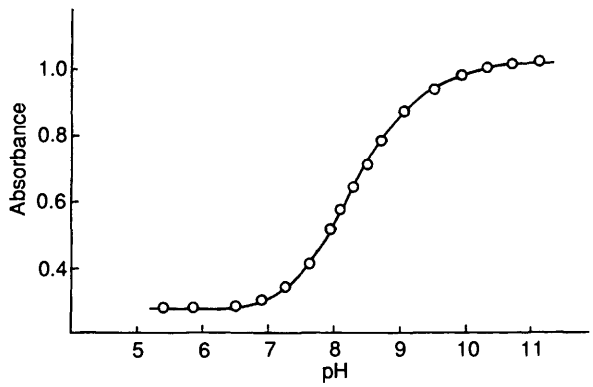


Fig. 2. Absorbance (at 325 nm) *vs.* pH plot for isatoic anhydride at 25 °C (μ = 1.0, KCl); $pK_a = 8.25$.

Reaction of N-*Methylisatoic Anhydride with Amines.*—Since this substrate cannot undergo ring opening to give an isocyanate intermediate it was important to discover its reactivity with amines in order to determine the magnitude of the rate constants for the reaction between neutral substrate and amine alone. These are listed in Table 1. It is clear from the results above with HO^- that **7** (X = H, R = Me) provides a good model for the un-ionized isatoic anhydride. Any rate difference then observed for **1** can be attributed to reaction with the conjugate base.

Preliminary experiments established that the reaction is second order overall, and first order each in the anhydride and in the amine free base (see Table 2). The products obtained were the corresponding amides **3** resulting from amine attack at the

Table 2. Second-order rate constants for the reaction of isatoic anhydride (k_2) and its conjugate base (k_3) with amines.[a]

Amine	$10^{11}K_{a_2}$[b]	k_2/dm^3 mol^{-1} s^{-1}	k_3/dm^3 mol^{-1} s^{-1}
$EtNH_2$	2.24	190	—
Pr^iNH_2	2.34	16	4.6×10^{-2}
Bu^tNH_2	2.08	0.08	2.6×10^{-3}
Et_2NH	1.05	22	3.3×10^{-1}

[a] At 25 °C (μ = 1.0, KCl); [b] Of the amine.

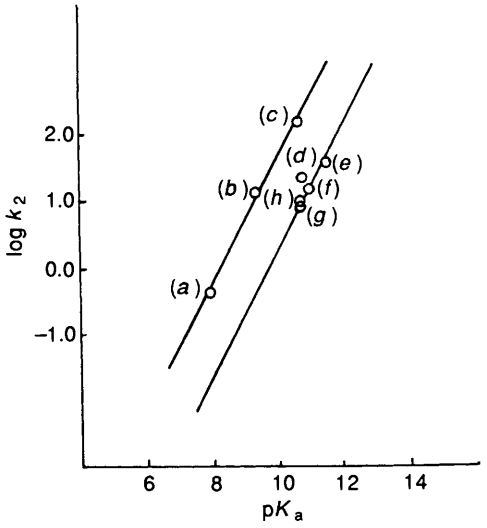


Fig. 3. Brønsted plot of log k_{amine} (k_{amine} is the second-order rate constant for the reaction of free amine with *N*-methylisatoic anhydride) *vs.* amine pK_a. The amines used are as follows: (*a*) glycine ethyl ester; (*b*) ammonia; (*c*) methylamine; (*d*) ethylamine; (*e*) piperidine; (*f*) diethylamine; (*g*) isopropylamine; (*h*) dimethylamine.

'anhydride' carbonyl (C-4). No upward curvature (typical of the behaviour shown by aliphatic esters),[9] attributable to the incursion of a term in the rate law proportional to [amine],[2] was noted, even at high [amine]. The results obtained are summarized in terms of a Brønsted plot of log k_{amine} [where k_{amine} is the second-order rate constant for reaction of the free amine with **7** (R = Me, X = H), obtained from the observed rate of reaction and corrected for hydrolysis against pK_a of the amine]. The observed data are correlated by a line of slope (β_{nuc}) = +1.0, and a second line (drawn with the same slope in Fig. 3) is used to correlate the data for secondary amines. Interestingly the more bulky amines (such as Pr^iNH_2) have a reactivity closer to that of the secondary rather than the primary amines. The β_{nuc} value obtained is typical for the aminolysis of simple carbonyl compounds such as *p*-nitrophenylacetate (usually in the range +0.8 to +1.2);[10] however secondary amines are normally observed to react *more* rapidly than primary amines of the same pK_a and the observed (Fig. 3) sensitivity to steric effects (even with Pr^iNH_2) is also unusually large.

Reaction of Isatoic Anhydride with Amines.—The initial experiments were carried out with a range of primary and secondary amines as nucleophiles at a constant pH (9.0). The results obtained show wide scatter and prompted a more detailed analysis of the variation in the rates of aminolysis with changing amine concentration and pH.

A series of buffer dilution plots (for methylamine as nucleophile) is shown in Fig. 4. It is clear that the observed

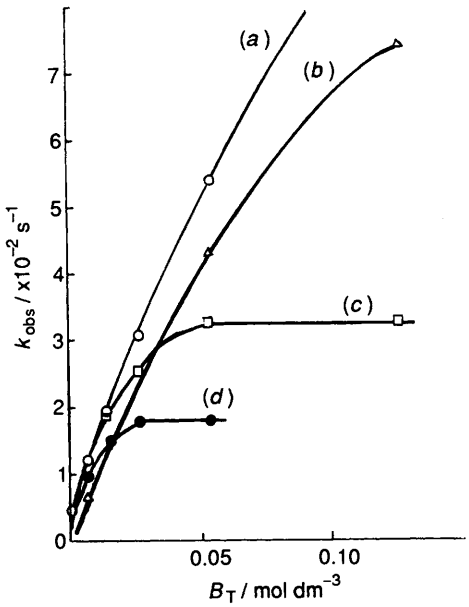
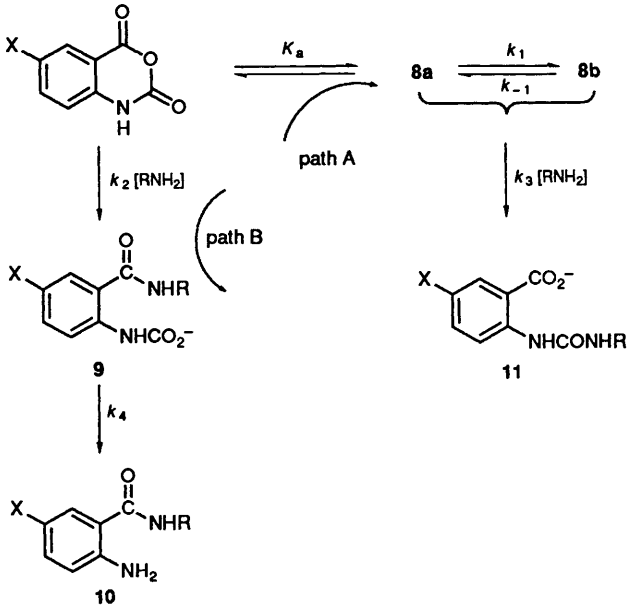


Fig. 4. Plot of the observed rate constants for the aminolysis of isatoic anhydride in methylamine buffers at 25 °C (μ = 1.0, KCl) and varying pH: (*a*) pH 8.0; (*b*) pH 8.3; (*c*) pH 8.7; (*d*) pH 9.0.

rate does not vary in a linear fashion with amine concentration but tends to a concentration independent 'plateau'; the plateau is reached at lower amine concentration when the pH of the reaction medium is high. A plot of the concentration independent 'plateau rate' against hydroxide ion (not shown) gives an inverse dependence.

Several explanations for this behaviour are possible. Two paths (paths A and B), involving a change in the rate-determining step with a change in pH and in amine concentration, are shown in Scheme 3. The key experiments which confirmed path



Scheme 3.

B are given in the Experimental section. This shows that at high [RNH_2] a new species, which is not the anion **8a**, is formed within the mixing time of the solutions. The intermediate formed, however, has the expected characteristics of the

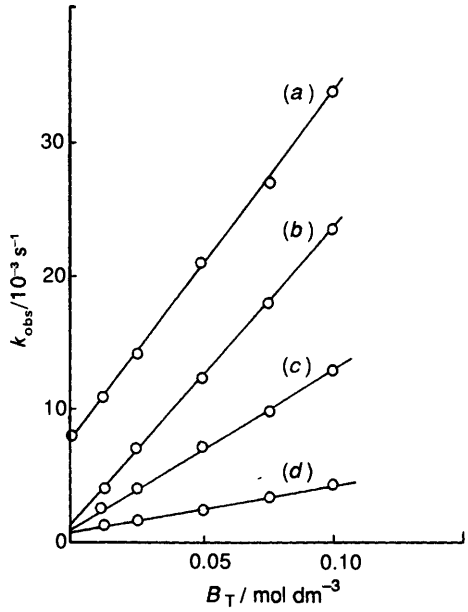
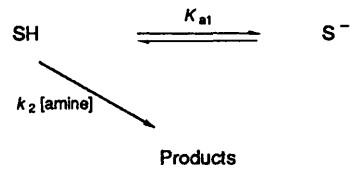


Fig. 5. Plot of the observed rate constants for the aminolysis of isatoic anhydride in diethylamine buffers at 25 °C (μ = 1.0 KCl) and varying pH: (*a*) pH 11.5; (*b*) pH 11.0; (*c*) pH 10.5; (*d*) pH 9.0.

carbamate **9**; thus decarboxylation of **9** to **10** is acid dependent while the rate constants for the subsequent reaction (the 'plateau' rates in Fig. 4) are comparable to those expected for a simple substituted *N*-phenylcarbamate.[11,12]

No change over in the rate-determining step was, however, apparent with ethylamine or diethylamine buffers as the observed rates of aminolyses were proportional to amine concentration (see, for example, Fig. 5) over the entire range. The behaviour of these and two other amines was investigated in some detail.

(*a*) *Ethylamine.* The variation in the observed first-order rate constants for the aminolysis of isatoic anhydride in 1.0 mol dm^{-3} total ethylamine concentration as a function of pH is shown in Fig. 6. This shows a maximum at pH 9.5 and the rate decreases in more acidic and basic media. These results are consistent with the reaction only occurring between the neutral amine (amine) and neutral substrate (SH) (see Scheme 4). Since both amine



Scheme 4.

and SH have pK_as in the region studied, the observed rate of aminolysis ($k_{obs} - k_{hydr}$) gives rise to the typical bell-shaped dependence of eqn. (3); this closely fitted the data (see solid

$$k_{obs} - k_{hydr} = k_2K_{a_2}a_H[\text{amine}]/[a_H^2 + a_H(K_{a_1} + K_{a_2}) + K_{a_1}K_{a_2}] \quad (3)$$

line in Fig. 6). We conclude, therefore, that over the pH range 7–11, reaction only occurs between free ethylamine and the neutral isatoic anhydride.

(*b*) *Isopropylamine.* This amine shows broadly the same behaviour except that the rate of aminolysis, instead of decreasing at high pH, tends to become pH independent. These data are correlated by the empirical kinetic Scheme 5 which

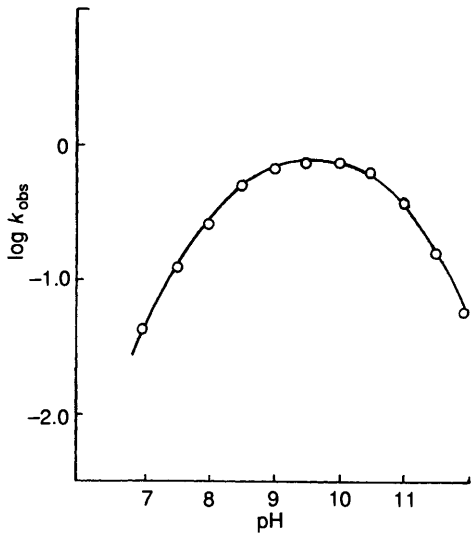
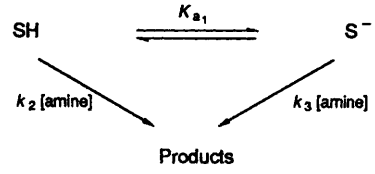


Fig. 6. Observed pseudo-first-order rate constants for the aminolysis of isatoic anhydride in 1.0 mol dm^{-3} ethylamine buffers at 25 °C (μ = 1.0 KCl). The plot was obtained using eqn. (3) with k_2 = 1.88 × 10^2 dm^3 mol^{-1} s^{-1}, K_{a_1} = 5.62 × 10^{-9}, and K_{a_2} = 2.24 × 10^{-11}.



Scheme 5.

implies that the competing reaction occurs with the amine and both the neutral isatoic anhydride and its anion (S$^-$). The derived eqn. (4) is fitted to the data with k_2 = 15.9 dm^3

$$k_{obs} - k_{hydr} = \frac{k_2K_{a_2}a_H[\text{amine}]}{a_H^2 + a_H(K_{a_1} + K_{a_2}) + K_{a_1}K_{a_2}} + \frac{k_3K_{a_3}[\text{amine}]}{a_H + K_{a_2}} \quad (4)$$

mol^{-1} s^{-1}, k_3 = 4.64 × 10^{-2} dm^3 mol^{-1} s^{-1}, K_{a_1} = 5.62 × 10^{-9} and K_{a_2} = 2.34 × 10^{-11}. At high pH direct hydrolysis of isatoic anhydride is the dominant reaction; aminolysis therefore contributes very little to the overall reaction of the conjugate base at high pH.

(*c*) *t-Butylamine.* The pH dependence of aminolysis of this amine is shown in Fig. 7. Although the appearance of the curve is different, this is due to the dominance of the term involving the reaction of the neutral amine with the anion, S$^-$. The values of k_2 and k_3 required to fit eqn. (4) are 7.88 × 10^{-2} dm^3 mol^{-1} s^{-1} and 2.59 × 10^{-3} dm^3 mol^{-1} s^{-1} respectively (solid line, Fig. 7).

(*d*) *Diethylamine.* This secondary amine shows broadly the same behaviour as t-butylamine in that the dominant aminolysis reaction is between the free amine and the conjugate base of the substrate. The data (Fig. 8) are correlated with eqn. (4) using k_2 = 22.6 dm^3 mol^{-1} s^{-1} and k_3 = 0.33 dm^3 mol^{-1} s^{-1}.

Table 2 summarises these data. It is clearly seen that although all four amines have about the same basicity, there is marked variation in the magnitude of both the k_2 and k_3 terms. Steric accessibility of the two reaction sites is the dominant factor with these bulky amines and since reaction with the neutral substrate is most sensitive, reaction with the conjugate base of isatoic anhydride becomes dominant only (*a*) at high pH and (*b*) with

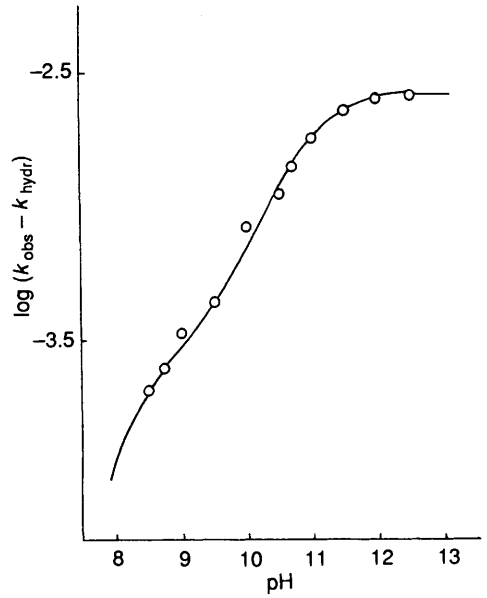


Fig. 7. Observed first-order rate constants for the aminolysis of isatoic anhydride in 1.0 mol dm^{-3} t-butylamine buffers as a function of pH at 25 °C (μ = 1.0, KCl). The plot was obtained using eqn. (4) with $k_2 = 7.88 \times 10^{-2}$ dm^3 mol^{-1} s^{-1} and $k_3 = 2.59 \times 10^{-3}$ dm^3 mol^{-1} s^{-1}.

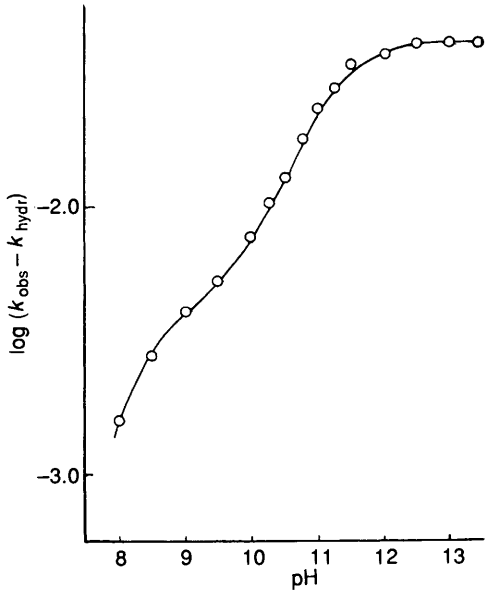


Fig. 8. Observed first-order rate constants for the aminolysis of isatoic anhydride in 0.1 mol dm^{-3} diethylamine buffers as a function of pH at 25 °C (μ = 1.0, KCl). The plot was obtained using eqn. (4) with $k_2 = 22.58$ dm^3 mol^{-1} s^{-1} and $k_3 = 3.3 \times 10^{-1}$ dm^3 mol^{-1} s^{-1}.

the more sterically hindered nucleophiles. It is interesting that the qualitative results of Staiger and Miller,[13] derived from product studies, are in general agreement with this conclusion.

5-Nitroisatoic Anhydride.—Since reaction of the conjugate base of isatoic anhydride only becomes dominant in limited circumstances at high pH (and with the more bulky amines), the more acidic 5-nitro derivative (**7**; R = H, X = NO_2) was also investigated.

This substrate is markedly more acidic; Fig. 9 shows a plot of log k_{obs} for hydrolysis as a function of pH which gives a pK_a of 6.7 (a similar value was determined spectrophotometrically). However, the pH independent plateau rate is much the same as for isatoic anhydride (see Fig. 1); although the concentration of the neutral form is less at high pH, this is almost compensated by the higher reactivity of the 5-nitro derivative towards HO^-.

Aminolysis of **7** (R = H, X = NO_2) was investigated as a function of amine concentration and pH. Buffer dilutions using methylamine at pH 9.7 showed strict linearity; the changeover observed with **1** was not seen. Fig. 10 shows the relationship with pH using a constant concentration (0.05 mol dm^{-3}) of the amine. Again a bell-shaped dependence (neutral anhydride reacting with the free amine) dominates its reactivity; however, a pH independent rate [free amine reacting with the conjugate base **8** (X = NO_2)] is apparent at high pH.

The latter reaction was investigated in more detail using the amines listed in Fig. 11. It was not necessary to measure in each case the pH dependence of k_{obs} over a wide range since at a sufficiently high pH (generally > 11), $k_{obs} - k_0$ is independent of pH. The results obtained, which are shown in the form of a Brønsted plot in Fig. 11, reveal that k_3 does show a small dependence on the basicity of the amine (the slope, β_{nuc}, is +0.31). This result is interesting in that a similar value was obtained (β_{nuc} = 0.30) for the reaction of amine bases with phenyl isocyanate[14] and with cyanic acid.[15] This provides good evidence that the reaction with the anion **8** occurs *via* the *o*-carboxy isocyanate **8b**. In addition, the relative reactivities of HO^- to amine are similar in all three systems.

In summary, reaction of isatoic anhydride with amines occurs mainly (and with *N*-methylisatoic anhydride exclusively) at the C-4 position leading to formation with amines of *o*-amino substituted benzamides **3**. Reaction at the other carbonyl centre (C-2) occurs *via* the isocyanate (which is in equilibrium with the anion, the major species present at pH > 8.25). The two modes of reaction with nucleophiles show a distinctly different sensitivity to steric effects and to the basicity of the nucleophile, which can be exploited to direct nucleophilic attack at either site. Reaction at the normally disfavoured C-2 site can also be enhanced by substituents (such as NO_2) which increase the concentration of the anion of isatoic anhydride in the pH range where amines are present in the reactive free base form. The use of solvents which reduce the pK_a of isatoic anhydrides will also favour reaction *via* the isocyanate, particularly when combined with amines of relatively low pK_a.

Experimental

General.—All materials used were available commercially. Isatoic anhydride, 5-nitroisatoic anhydride, and *N*-methylisatoic anhydride were recrystallized from ethanol before use and dried *in vacuo* over P_2O_5.

Inorganic materials used for kinetic measurements were AnalaR grade. Amines were purified by distillation from KOH (liquid amines) or by recrystallizations of the hydrochloride salts from ethanol or ethanol–water. Standard solutions of KOH and HCl were prepared from M and B Volucon ampoules. Deionized water was twice distilled from an all-glass Fi-stream apparatus.

Kinetic Method.—Kinetic data were obtained spectrophotometrically in the UV region. With buffered solutions either a Beckmann Model 25 or a Perkin-Elmer PE124 was used, while unbuffered reactions were examined using a Cary 14 fitted with a pH stat as previously described.[2] Kinetic runs were initiated by adding 10 cm^3 of a solution of the substrate (*ca.* 10^{-2} mol dm^{-3}) in dioxane to a quartz cell containing the buffer solution (3 cm^3) equilibrated at 25 °C. The resultant log *A vs. t* plots were strictly first order and gave good infinity values; the rate constants were calculated graphically using the experimental value of the absorbance after ten half-lives.

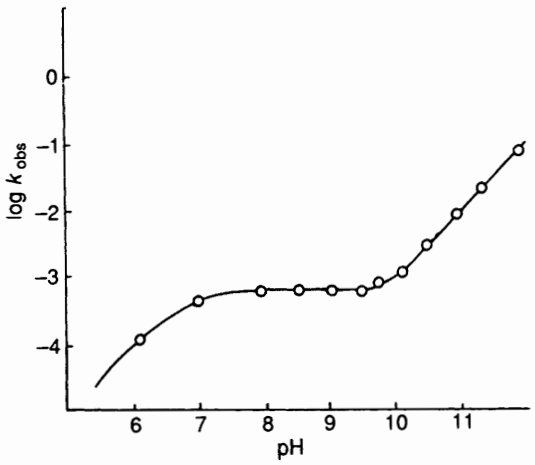


Fig. 9. Plot of the log of the observed first-order rate constants for the hydrolysis of 5-nitroisatoic anhydride *vs.* pH at 25 °C (μ = 1.0, KCl).

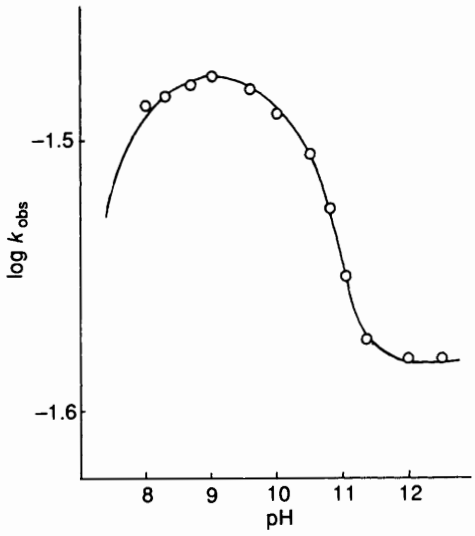


Fig. 10. Plot of log ($k_{obs} - k_{hydr}$) *vs.* pH for the aminolysis of 5-nitroisatoic anhydride in 0.05 mol dm^{-3} methylamine buffers at 25 °C (μ = 1.0, KCl). The plot was obtained using eqn. (4) with k_2 = 5.86 × 10^3 dm^3 mol^{-1} s^{-1}, k_3 = 5.16 × 10^{-1} dm^3 mol^{-1} s^{-1}, K_{a_1} = 1.99 × 10^{-7} and K_{a_2} = 2.4 × 10^{-11}.

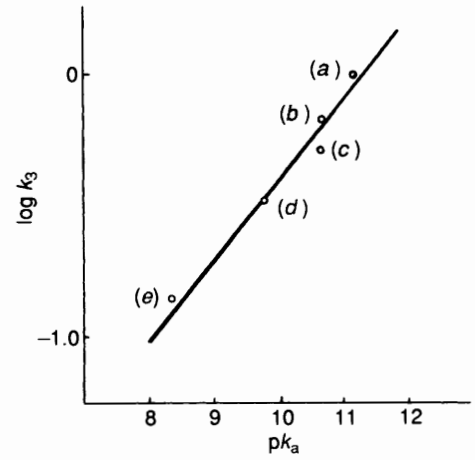


Fig. 11. Brønsted plot for the reaction of the conjugate base of 5-nitroisatoic anhydride (**8**; X = NO_2) with a series of amines: (*a*) piperidine; (*b*) ethylamine; (*c*) methylamine; (*d*) glycine; (*e*) morpholine.

Demonstration of Change in the Rate-determining Step.—A typical series of experiments is as follows. A stock solution of isatoic anhydride (10^{-2} mol dm^{-3}; 10 mm^3) in dry dioxane was added to a 0.05 mol dm^{-3} borax buffer (2.0 cm^3) the pH of which had been adjusted to 9.35. The absorbance *A* of the solution at 260 nm [where the anion **8** (X = H) has a strong absorbance] was noted and extrapolated back to the time of mixing. The same stock solution (10 mm^3) was added in a second experiment to a solution (2.0 cm^3) of methylamine (0.0054 mol dm^{-3}) and borax (0.05 mol dm^{-3}) at pH 9.35. The absorbance at 260 nm (extrapolated to zero time) was the same as observed in the first experiment; note that under these conditions amine attack on isatoic anhydride (see Scheme 3 and Fig. 4) is rate determining. In the third experiment, 10 mm^3 of the same isatoic anhydride stock solution were added to the borax buffer (2.0 cm^3, 0.005 mol dm^{-3}, pH 9.35) containing 0.054 mol dm^{-3} methylamine. The initial absorbance obtained was <25% of that observed in the first two experiments. Note that at the methylamine concentration used in the third experiment, the second step (decarboxylation of **9**) is rate determining. This was confirmed using several (high) initial amine concentrations in the pH region 8.5–10. In the pH region where the formation of the intermediate **9** was comparable to the rate of decarboxylation of the carbamate, the formation of **9** was followed at 280 nm, where the second reaction showed a minimal spectral change.

Product Analysis.—Although no detailed product analysis was carried out as part of this kinetic study it was confirmed in two cases (using ethylamine and t-butylamine as nucleophiles) that the product UV spectra corresponded to those obtained on mixing amounts of the amide and urea implied by the kinetic results. The authentic samples were prepared from isatoic anhydride and separated according to the method of Staiger and Wagner,[4] and had m.p. and IR data in agreement with literature values: *N*-ethylanthranilamide, m.p. 103–104 °C (lit.,[16] 104–105 °C); 2-(N^1-ethylureido)benzoic acid, m.p. 189–190 °C (lit.,[4] 189 °C); *N*-t-butylanthranilamide, m.p. 120–123 °C (lit.,[17] 123–125 °C); 2-(N^1-t-butylureido)benzoic acid, m.p. 173–175 °C (lit.,[4] 174–176 °C).

The UV spectra of the products could be reproduced by mixing **10** (R = Et, X = H) and **11** (R = Et, X = H) in the ratio 1:0 (at pH 9.0) and 1:0.05 (at pH 11.0) for ethylamine; for t-butylamine the ratios used were 1:2.24 (at pH 9.0) and 1:12.5 (at pH 11.0) for **10** (R = Bu^t, X = H) and **11** (R = Bu^t, X = H) respectively.[17]

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